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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/027,671	02/23/1998	ALAN K. SMITH	4292-0048-55	3507

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
06/28/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	09/027,671	SMITH ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *95-98,100,102,108,110 and 112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *95-98,100,102,108,110 and 112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 04/30/07 is acknowledged.

Claims 95-98, 100, 102, 108, 110 and 112 are pending.

2. Applicant's submission of Terminal Disclaimer has obviated the previous rejection of claims 95-98, 100, 102, 108, 110 and 112 under the judicially created doctrine of obviousness-type double patenting over claims 1-18 of U.S. Patent No. 6,835,5662.

3. Applicant's submission of Declaration under 37 C.F.R 1.132 by Dr. Smith, indicating that authors of Smith et al., prior art paper Gorgas, Jensen, Hastie and Brott were working under the direction and supervision of the inventor of the instant application, Dr. Smith, has obviated the previous rejection of claims 95-98, 100, 102, 108, 110 and 112 under 35 U.S.C. 103(a).

Claims 95-98, 100, 102, 108, 110 and 112 read on method of obtaining human cells with enhanced biological function comprising culturing at least one of human osteoblasts, osteoclasts and human T cells in a liquid culture medium which is replaced at a rate of at least 50% to 100% daily for the cell are under consideration in the instant application.

In view of the amendment, filed 04/30/07 the following rejections remain:

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 95-98, 100, 102, 108, 110 and 112 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a method of obtaining a human T lymphocytes with enhanced replicative potential comprising culturing said cells under conditions including replacement of a liquid culture at a rate of from 50% to 100 % daily replacement

compared to replicative potential of a human T lymphocytes culturing ex vivo under conditions which do not include replacement of the liquid culture medium, does not reasonably provide enablement for a method for obtaining a human cells with enhanced of *any* biological function , comprising enhanced replicative potential, wherein said human cells are recited in claim 95, compared to the biological function of said cells cultured ex vivo under conditions which do not include replacement of the liquid culture medium, claimed in claims 95-98, 100, 102, 108, 110 and 112. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed on 11/04/05.

Applicant's arguments, filed 04/30/07 have been fully considered, but have not been found convincing.

Applicant asserts that (i) amended claims include enhanced replicative potential as an enhanced biological function; (ii) Declaration by Dr. Smith indicating that enhanced replicative potential of osteoclasts and osteoblasts were obtained when said cells were incubated as claimed.

Contrary to Applicant's assertion, it is noted that the amended claim 95 now recites " wherein the enhanced biological function comprise enhanced replicative potential".

"Comprising" is considered open-ended claim language and thus may includes any additional non disclosed function. Moreover, it is noted that the instant Specification broadly defined biological function as " the ability of a cell population to carry outs its biological mission, i.e. to performed its recognized biological purpose *in vivo*" (see overlapping pages 10- 11 of the instant specification in particular). As has been stated in the previous Office Action, the specification only discloses detailed *in vitro* studies wherein human T lymphocytes and human dendritic cells grown under continuous perfusion of medium resulted in high density of concentrations, i.e. enhanced replicative potential (see Example 1-3 in particular) The specification does not adequately teach how to effectively obtained a human cells with enhanced of *any* biological function , wherein said human cells are recited in claim 95 compared to the biological function of said cells wherein said cells cultured ex vivo under conditions which do not include replacement of the liquid culture medium. Moreover, the Specification does not even define what biological function, besides stimulating activity of dendritic cells *in vitro,* would be enhanced. Applicant has not exemplified any *in vivo or in vitro* studies, wherein claimed method results in enhanced of *any* biological function of human cells recited in claim 95.

With regards to Applicant statement that Declaration by Dr. Smith indicating that enhanced replicative potential of osteoclasts and osteoblasts were obtained when said cells were incubated as claimed.

It is noted that said Declaration indicated that cells growing under static culture (0% exchange) has been compared with cells growing under condition of continuously culture exchange (12, 25, 35 and 50 % exchange) on days 7, 12 and 19 (see page 2 of Declaration by Dr. Smith submitted on 04/30/07). In other words, cells that were grown up to 7, 12 or 19 days without medium exchange have been compared with cells grown under condition wherein culture medium has been constantly exchange. It is well know to one skilled in the art that maintaining cells under optimal growth conditions requires medium exchange on a daily basis and at appropriate cell density. (see for example Basic Cell Culture protocols, ed. Helgason and Miller, 2005, page 219). Moreover, in the Manual of Cell Culturing techniques ed. Stacey and Hockley, 2000, page 24) it is explicitly sated that maintaining cell under optimal growth conditions can be very difficult in tradition tissue culture flasks and **failure to provide adequate changes of culture medium** and failing to passage cells at appropriate times can **cause a range of deleterious effects in the cells** that might result in changes in the characteristics of the culture which may be permanent and **alter the response of cells in bioassays or other applications** (emphases added). In other words one skill in the art would know that cells growing under static condition (0% exchane) for more than 7, 12 or 19 days would have different biological function compare to cells grown under condition of continuously culture exchange.

Since there are no *in vivo* studies or data in the specification to show the effectiveness of maintaining or preserving any enhanced biological function of human cells recited in claim 95, it is unpredictable as to how to correlate *in vitro* results with *in vivo* use. Although the Specification describes certain *in vitro* experiments, there is no correlation on this record between *in vitro* experiments and *in vivo* data of the method of obtaining and maintaining an enhanced any biological function of human cells recited in claim 95 comprising replacement of a liquid culture medium at a rate of from 50% to 100% daily replacement . It is not enough to rely on *in vitro* studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to efficacy in humans or animals.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed a method for obtaining a human cells with enhanced of *any* biological function , wherein said human cells are recited in claim 95, compared to the biological function of said cells cultured ex vivo under conditions which do not include replacement of the liquid culture medium, claimed in claims 95-98, 100, 102, 108, 110 and 112 in a manner reasonably correlated with the scope of the invention. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 95-98, 100, 102, 108, 110 and 112 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,994,126 for the same reasons set forth in the previous Office Action, mailed on 11/04/05.

Applicant's arguments, filed 04/30/07 have been fully considered, but have not been found convincing.

Applicant asserts that claims of US Patent 556 are directed to dendritic cells and the instant claims are define other cell types.

Contrary to Applicant's assertion, it is noted that the instant claims are rejected under 35 USC103 not under 35 USC102. Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

In the instant case, US Patent '126 teaches a method of obtaining lineage committed human cells comprising culturing said cells under physiologically acceptable liquid culture conditions including replacement of the liquid culture medium at a rate and for a time sufficient to obtained

cells suitable for various immunological intervention and treatment of diseases and transferring said cultured cells into a patient (see entire document, column 12, lines 55-65, column 13, lines 10-25, column 15, line 54-65 and column 21, line 29-35 in particular). US Patent '126 teachers that media replaced every other day for about $5x10^5$ cells/ml culture(see column 17, lines 60-65 and Example 1 in particular). US Patent '126 teachers that culture medium is any culture medium suitable for growing human cells for example RPMI (see column 16, lines 15-65 and Examples 1 and 2 in particular) . It is noted that US Patent '126 teaches does not explicitly teaches that said cells have an enhanced biological function as compared to the function of the lineage committed cell cultured *ex-vivo* under conditions which do not include replacement of the liquid culture. However, it is noted that the referenced cells are human cells that have been cultured under the same culturing conditions as claimed thus obviously would have an enhanced biological function *in vitro*. Moreover, it is noted that the specification on page 11, first paragraph disclosed that one skill in the art will readily appreciate that the term "biological function" refers to ability of a cell population to carry out its biological missions, i.e. for example the ability to proliferate leading to development/regeneration of tissue. Thus, it would be immediately obvious to one skill in the art that the referenced cell with enhanced biological function includes the ability to generate tissue. It is also noted Discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. " The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art". See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed.

The claimed invention differs from the reference teaching in that US Patent '126 do not explicitly teach that the culture medium is replaced daily at the rate of at least 50% to 100% for a density from $1x10^4$ to 1 10^7.

It is noted however, that prior art references teach a culturing condition, wherein the medium is continuously perfused. In other words, they teach the culturing condition wherein culture medium is replaced. Thus, it would require only routine experimentation for a person of ordinary skill in the art to determine the optimum rate of replacement of the medium, i.e. at a rate of from 50% to 100% and a density from $1x10^4$ to 1 10^7 . Moreover, as has been discussed supra, at the time the invention was made, one skill in the art would know that maintaining cells under optimal growth conditions requires medium exchange on a daily basis and at appropriate cell density. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only

routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

6/22/07